

vated, however, and therefore could not signal transcription of androgen-dependent genes, which disrupted sexual development. Vinclozolin was the first chemical reported to have an anti-androgenic effect.

The EPA investigators and molecular biologists from the University of North Carolina at Chapel Hill began to compare their data with Guilette's and months later invited Guilette to the EPA to examine the results. The team found that DDE, the primary metabolite of DDT, shrunk sex organs in male rats by up to 20% in four days. And pregnant rats exposed to DDE gave birth to male rats with female sexual characteristics.

Guilette and the rest of the scientific world were surprised by the results, published in *Nature* on June 15. "There was quite significant binding that helps explain what we saw in the alligators," says Guilette. "I'm rethinking the whole concept of hormone receptor specificity. It's much more complex than we realized." Guilette noted that because some minor isomers of DDT are clearly estrogenic, DDT and its metabolites are now known to affect both estrogenic and androgenic hormone action.

DDE's anti-androgenic effects may help explain recent adverse changes in male reproductive health, such as decreasing sperm counts in various parts of the world, and increases in testicular cancer and cases of abnormal development of the penis and testis. The work also raises the question of how chemicals can act simultaneously as agonists and antagonists for both estrogen and androgen, says Kenneth Korach, an NIEHS researcher who was involved in creating an estrogen knock-out mouse. Elizabeth Wilson, a University of North Carolina at Chapel Hill investigator working with Kelce, is researching whether the androgen receptor forms a heterodimer, binding both DDE and androgen. The dose response of DDE would be critical in this case, she says.

Although DDT was banned in the United States in 1973, DDT and its metabolites persist in the environment (it has a half-life of up to 100 years), and it is still used to control malaria in some countries such as Mexico and Brazil, and in some areas of Africa.

The EPA/UNC team reported that the concentration of DDE needed to inhibit androgen receptor transcriptional activity in cell culture or to affect newborn rat pups is analogous to levels found in other instances of DDT contamination including Guilette's Florida alligator eggs and in kidneys of still-born babies in the United States in the mid-1960s, when DDT was still being used.

Scientifically, the study offers more questions than answers. It raises the issue of the adequacy of testing manufactured chemicals

## EHPnet

In war and football, it's often said that the best defense is a good offense. This same philosophy is the basis for a World Wide Web site aimed at improving the environment through pollution prevention. Enviro\$ense (URL:<http://wastenot.inel.gov:80/envirosense/>), which is maintained at the Idaho National Engineering Laboratory, is funded by the EPA and the Strategic Environmental Research and Development Program (SERDP), a joint effort of the Department of Defense, the Department of Energy, and the EPA that supports environmental quality research, development, demonstration, and applications programs.

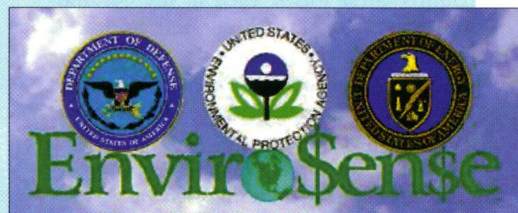
Eight hyperlinks on the Enviro\$ense homepage offer a vast array of information in categories such as news and resources, pollution prevention programs from the local to the federal level, international programs, technical research and development, compliance and enforcement, and more.

For example, the news hyperlink connects users to information such as a Pollution Prevention Directory, several hotlines and clearinghouses, the National Consortium for Environmental Education and Training's Environmental Education Link (a gopher site that offers access to teaching resources including instructional materials, articles, databases, and grant information), and the National Pollution Prevention Center for Higher Education.

Federal laws, regulations, environmental activities, and presidential executive orders, and both state and local pollution prevention servers may be accessed through another hyperlink. The international resources hyperlink provides information on pollution prevention programs around the world by connecting to organizations such as the U.S. Agency for International Development's Environmental Prevention Protection Project, the Montreal Protocol (protection of ozone layer), the North American Free Trade Agreement, the Organization for Economic Cooperation and Development, and the United Nations Environment Program.

The technical research and development hyperlink provides access to case studies and fact sheets on EPA studies of commercial companies, as well as environmental research briefs, project summaries, and pollution prevention assessments. This link also connects to the EPA Office of Research and Development and a pollution prevention publications bibliography.

Perhaps the most innovative element of the site is an interactive search function that allows users to query the Solvent Alternatives Guide (SAGE), the Hazardous Solvent Substitution Data System (HSSDS), and the Department of Defense Pollution Prevention Technical Library. SAGE is a logic-tree system that evaluates a manufacturer's current operating scenario and then identifies possible alternative surface-cleaning solvent chemistries and processes that best suit the operating and material requirements. HSSDS is an on-line system of information on alternatives to hazardous solvents that contains product information, material safety data sheets, and other related information. Also available on this site is access to the Department of Defense Ozone Depleting Chemical/ Substance Information.



for hormonally active compounds. "Past regulatory testing was insensitive to these kinds of problems," says Kelce. "We are only now beginning to appreciate what tests need to be conducted."

Guilette also wonders about the effect of an anti-androgen on females: "If it modifies the estrogen-androgen ratio in women, increasing their estrogen, it could result in increased breast cancer and like diseases." Kelce says he has identified 20 other chemicals that have anti-androgenic effects. Although he says he can't release the list yet, he indicated that none of them is currently banned.

## The Immortality Enzyme

Telomerase, an enzyme that gives some cells a permanent stay of execution, appears to play a role in lung cancer progression, according to a study in the June 25 issue of the *Journal of the National Cancer Institute*. Jerry Shay and his colleagues at the University of Texas Southwestern Medical Center at Dallas and at the Hiroshima University School of Medicine found telomerase activity in approximately 80% of the 136 primary lung cancer tissues they tested, versus only about 4% of 68 adjacent normal tissue samples. Of the 136 primary lung cancer samples, all 11 of the small cell lung can-

cers (SCLC) showed telomerase activity, while telomerase activity varied in non-small cell lung cancers (NSCLC).

Normally, telomerase is inactive in somatic cells, which die naturally after a number of cell divisions. Each time a chromosome is reproduced, the telomere, a small part at the end of the chromosome, is lost. In order to counter these losses, each of the chromosome's telomeres carries repeating nucleotide sequences. However, once those sequences are used up, the cell stops dividing and dies. Cells that need to continue to reproduce, such as germ line reproductive cells, carry telomerase, a DNA polymerase which adds repeating nucleotide sequences to the shortened telomeres. Previous studies have also found telomerase activity in malignant tumors of numerous cell types including breast, prostate, colon, skin, and brain, suggesting that the enzyme allows cancer cells to continue to divide.

The reactivation of telomerase may occur at either of two stages of cell death, mortality stage 1 (M1) or mortality stage 2 (M2). During M1, cells lose their ability to divide, a state known as senescence. The malfunction of a tumor-suppressor gene or the mutation of an oncogene might transform a cell, allowing it to avoid senescence. However, although such defects extend the cell's life span, it will eventually die. During M2, cells reach a point known as crisis, in which most cells die; however, the survivors are immortal and capable of unlimited proliferation.

The presence of NSCLC tumors containing both mortal and immortal cells suggests that the immortalization of an existing tumor cell is rare, requiring two separate events and occurring after many cell divisions. In SCLCs, cells show signs of having already undergone the number of divisions and chromosomal changes necessary for the reactivation of telomerase before becoming cancerous.

Shay and his colleagues observed variations in telomerase activity that may reflect characteristics of the cells or the ratio of mortal to immortal cells within the tumors. However, although levels of telomerase activity varied dramatically among some of the samples tested, immortalized lung cancer cell lines all showed similar activity, whether SCLC or NSCLC. The study's authors cautiously suggest that once a lung cell is immortalized, it achieves a set level of telomerase activity no matter what its type.

The absence of telomerase activity in some

tumors may indicate that they consist entirely of mortal cells. A previous study, published in *Science*, found that benign fibroid tumors did not have telomerase activity. According to Shay's study, "If cancers that have mortal cells exist, their growth might be self-limiting in contrast to those that consist of immortal cells," a possible reason why SCLCs are the most difficult lung cancers to treat. This distinction between cell populations with telomerase activity and those without it may serve as the basis for tests to predict the cells' capacity for continued proliferation and, therefore, the disease's severity. Telomerase activity might even be found in cells obtained from a patient's lung wash, a procedure Shay used in his study and one which is already commonly used for other



**Solid gold silos?** Two containers at the Fernald nuclear plant, slated for clean-up, hold medically priceless amounts of radium.

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types of lung cancer diagnostic tests.

Researchers are already searching for a drug that inhibits telomerase, in hopes of cutting short the lives of the most proliferative lung cancer cells. In the August 31 issue of *Science*, researcher Calvin B. Harley of Geron Corporation and his colleagues at Cold Spring Harbor Laboratory reported that they were able to produce reverse RNA that blocked the action of telomerase and caused HeLa cells, an experimental cancer cell line, to begin dying after 23–26 cell divisions. While Harley emphasizes that a drug able to mimic this effect may take years to find and develop, such a drug could prevent the spread of cancer without harming normal cells. In an interview with the Associated Press, Shay said, "This is the first laboratory proof that inhibiting of telomerase RNA will result in limiting cell division. . . . This is the most important next step in telomerase research."

In an earlier AP interview Shay pointed out that the existence of metastatic tumors lacking telomerase activity implies that there

are other immortalization mechanisms. According to molecular epidemiologist Curtis Harris of the National Cancer Institute, a mechanism that enabled cells to escape senescence would be one that bypasses the problem of shrinking telomeres, such as DNA recombination, probably a very inefficient mechanism. If drugs were developed to target telomerase, these alternate mechanisms of immortalization might come into play to allow tumor cells to escape senescence, says Harris. Even in those cells where telomerase inhibitors successfully prevented immortalization, any remaining supply of telomeric repeats would allow the cell to continue to divide for a finite period of time, with possible adverse consequences to the patient. In addition, other cells in the

body, such as stem cells and stomach cells, might be sensitive to telomerase inhibitors, leading to serious side effects.

## What a Waste

It may seem unusual for U.S. scientists and medical researchers to lobby strongly against a government program to clean up the contaminated Fernald nuclear plant in Ohio, but that's exactly what's happening. The Fernald plant, which processed uranium for nuclear weapons from 1951 to 1989, now has about 10,000 tons of radioactive waste contained in two special silos. Within this waste, however, is a medically priceless stockpile of radium as well as millions of dollars worth of gold and other precious metals. Scientists are arguing that

this radium, which is scheduled to be disposed of starting in early 1996, may be critical to saving the lives of cancer patients if a clinical trial that attempts to cure cancer with a radium-based monoclonal antibody is successful.

David Scheinberg, a medical oncologist at the Memorial Sloan Kettering Cancer Center, is enrolling patients in a clinical trial to test a new methodology that links a radium-based isotope, bismuth-213, to a monoclonal antibody to target cancer cells. The treatment is being tested on 10–20 patients who have acute myeloid leukemia (AML) or chronic myeloid leukemia (CML). In a preliminary experiment using a leukemia mouse model, the bismuth-213 antibody treatment led to remission of the diseases and longer survival rates. If the phase I trial scheduled for November is successful, it will be followed by a slightly larger study within a year of the phase I results. If further clinical trials show positive results and the treatment is approved by the FDA, it could potentially be